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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	GI5298A	3002

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/148,234	MOUTSATSOS ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.P.G.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/21/05 has been entered.

2. In the submission filed 6/21/05 claims 24-27 were amended. Currently claims 24-28 are pending and under examination. Any rejection of record in previous office actions not addressed herein is withdrawn.

Claim Rejections - 35 USC § 103

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens (DNA Cell Biol. 12:871-880 (1993), of record) in view of U.S. Patent No. 5,763,416 (hereinafter Bonadio, of record) and U.S. Patent No. 6,048,964 (hereinafter Lee, of record). The grounds for this rejection are maintained for the reasons of record in the previous office actions mailed 5/21/03 and 6/15/04.

5. Claim 24 was amended to add the limitation that the induced bone formation is "organized". Although this limitation was not present when the previous rejections were written, the limitation does not place any further restriction on the ability to apply the above-cited

references. Bonadio discloses at column 6, lines 15-30 the desire and ability to stimulate "proper bone growth" which appears to simply be another way to refer to bone formation as "organized". Further, Figure 8 shows that he bone formation induced by Bonadio is indeed organized, occurring only in the rejoin of the break. Thus the skilled artisan would have had a reasonable expectation that to practice the combined method of Ahrens, Bonadio, and Lee would have led to "organized" bone formation.

6. Claims24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens, Bonadio, and Lee as applied to claims 24-26 above, and further in view of U.S. Patent No. 6,291,206 (hereinafter Wozney, of record). The grounds for this rejection are maintained for the reasons of record in the previous office actions filed 5/21/03 and 6/15/04, also viewed in light of the new grounds presented in paragraph 5 above.

7. Claims 24-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens, Bonadio, Lee, and Wozney as applied to claims 24-27 above, and further in view of U.S. Patent No. 5,700,774 (hereinafter Hattersley, of record). The grounds for this rejection are maintained for the reasons of record in the previous office actions filed 5/21/03 and 6/15/04, also viewed in light of the new grounds of rejection presented in paragraph 5 above.

Response to Arguments

8. Applicant's arguments filed 6/21/05 have been fully considered but they are not persuasive. The response filed 6/21/05 essentially argues that: 1) Bonadio's assertion of the use of bone progenitor cells is not credible, this is addressed in a declaration by Dan Gazit; 2) that the Examiner assertion that the motivation to combine Ahrens and Bonadio only needs to take

into account a reasonable expectation of success is incorrect and that there is no motivation to combine the references with a reasonable expectation of success for inducing organized functional bone formation at a site of bone infirmity; 3) that Ahrens does not provide basis for the likelihood of *in vivo* success; 4) that Bonadio does not provide credible evidence that autocrine effects occur; 5) and that Applicants' *ex vivo* protocols provide unexpected benefits.

9. With regard to the Applicants' assertion that it is not a credible assertion made by Bonadio that stem cells can be targeted by the methods of Bonadio, this argument including the declaration by Dan Gazit filed 6/21/05, has been considered but is not considered persuasive. The declaration opines that Bonadio is not credible in the assertion that progenitor cells are targeted. This opinion is based on studies by Rebel *et al.* (Stem Cells 18:176-182 (2000), newly cited) and Zhao *et al.* (Blood 84:3660-3666 (1994), newly cited) which suggest that hematopoietic stem cells (HSCs) are drastically reduced in their ability to take up DNA. The conclusion drawn by Dan Gazit does not correspond to the data presented in the studies and the studies do not shed light on the ability of mesenchymal stem cells (MSCs) to take up DNA. Although the uptake by the HSCs is reduced in both studies, the HSCs are in fact capable of uptake. Further, the ability of HSCs to take up DNA is irrelevant with regard to the ability of MSCs to take up DNA. Additionally, the declaration ignores that Bonadio has also suggested the use of retroviral vectors. The evidence at hand would certainly suggest that retroviruses can indeed be used to infect MSCs. Later in the declaration a paper by Gazit *et al.* (J Gene Med 1:121-133 (1999), newly cited) is cited to suggest unexpected results. In this study however, retrovirus was used to infect the MSC cell line used (see page 123, column 1). Thus it would seem that MSCs can indeed be infected by retroviruses.

10. Furthermore the assertion by Bonadio is actually more than an assertion, it is a claimed limitation. As it is a claimed part of the invention of Bonadio, enablement of the claims are assumed absent evidence to the contrary. Lastly, as this is a rejection under 35 U.S.C 103, as obvious over a combination of references. Even if Bonadio was not able to specifically target stem cells, an assertion by Applicant that is not agreed to, Ahrens definitely teaches that MSCs can be transfected. This is the whole basis of Ahrens study.

11. The declaration also argues that as Ahrens shows *in vitro* differentiation and other studies show that differentiated bone cannot properly engraft. This argument is moot as there has been no suggestion that differentiated cells would be used in the cell therapy method.

12. Finally, the declaration opines that Gazit *et al.* establish that the *ex vivo* protocols provides unexpected results. This is based on the observation that only engineered progenitor cells, and not engineered CHO cells or 3 μg of recombinant BMP-2, lead to the formation of organized bone. This is an apples to oranges comparison and does not address the whether a combined method of Ahrens and Bonadio (and Lee) would lead to these results. The argument is based upon the assumption that Bonadio cannot successfully introduce DNA into stem cells. As argued above this is a false assumption which is somewhat immaterial as Ahrens can definitely introduce DNA into MSCs. The skilled artisan would not expect the transduced CHO cells to behave appropriately as CHO cells are not a bone-derived cell type.

13. The result suggesting that recombinant BMP-2 does not lead to appropriate repair would also have been expected. Yasko (J Bone Joint Surg Am 74-A: 659-670 (1992), of record) shows that low dose (1.4 μg) BMP-2 fails to lead to proper bone formation while high dose (11 μg) leads to proper bone repair (see Abstract and Figures of Yasko). The Gazit *et al.* study used 3 μg

of BMP-2. This certainly would be considered a low dose of BMP based on the study of Yasko, and Yasko teaches that low dose does not lead to efficient bone repair. Thus, the result in Gazit *et al.* that only BMP-2 transduced MSCs and not BMP-2 transduced CHO cells or low dose of recombinant BMP-2 lead to efficient bone repair is not an unexpected result

14. Regardless of the showing of unexpectedness by Gazit *et al.* the study by Gazit *et al.* does not address the issue at hand: would a combined teaching of Ahrens, Bonadio, and Lee lead the skilled artisan to expect successful organized bone repair? The methods of Bonadio alone teach that organized bone formation is achieved. This is evidenced by Fang (Proc Natl Acad Sci USA 93:5753-5758 (1996), of record) who teaches that when using the methods of Bonadio, organized bone repair is achieved (see particularly Figure 4). Since Bonadio's method leads to organized bone formation, what would lead the skilled artisan to any conclusion other than the reasonable expectation that the combined teachings of Ahrens, Bonadio, and Lee would have led to organized functional bone repair?

15. With regard to the argument that the Examiner's assertion that the motivation to combine Ahrens and Bonadio only needs to take into account a reasonable expectation of success is incorrect and that there is no motivation to combine the references with a reasonable expectation of success for inducing organized functional bone formation at a site of bone infirmity: it is indeed correct that the motivation to combine only needs to take into account a reasonable expectation of success. Applicants essentially assert that the combined teachings of Ahrens and Bonadio would not lead the skilled artisan to the alleged unexpected result of organized bone formation. First, organized bone formation has not been shown to be an unexpected result, as the teachings of Bonadio alone lead to organized bone repair (see above). However even if the result

was unexpected, it is unclear how this would alter the motivation to combine Ahrens with Bonadio (and Lee). The purpose of Bonadio's work was to promote bone repair and regeneration (see Bonadio columns 3-6), and naturally any person of skill in the art would desire proper functional bone.

16. Bonadio indeed contemplates *ex vivo* studies: "Isolated cells may be stimulated using the methods and compositions disclosed herein and, if desired, be returned to an appropriate site in an animal where bone repair is to be stimulated. In such cases, the nucleic-acid containing [sic] cells would themselves be a form of therapeutic agent. Such *ex vivo* protocols are well known to those of skill in the art" (Bonadio column 5, lines 14-19). Ahrens indeed teaches both the ability to introduce DNA into MSCs *in vitro*, the benefits of BMP-2 over BMP-4 (see Ahrens page 879, first full paragraph), and that MSCs transfected with BMP-2 or BMP-4 have the capacity to undergo osteogenesis (see below). Thus there is clearly a motivation to perform *ex vivo* studies, as claimed in the instant application, and a reasonable expectation of success. Whether or not better-organized bone is an unexpected result of the *ex vivo* protocols, a point in no way conceded, any benefit to performing an *ex vivo* protocol would be an inherent property of the type of assay. Since the combined teachings of Ahrens, Bonadio, and Lee show a motivation to perform *ex vivo* studies, in performing the studies, the skilled artisan would have necessarily observed any added benefits to an *ex vivo* protocol. Essentially, there is nothing in the claims to suggest that the instantly claimed method is in any way different from the method the skilled artisan would practice as a result of the combined teachings of Ahrens, Bonadio, and Lee.

17. Arguments in the response regarding points 3 and 4 of paragraph 8 above essentially amount to piecemeal analysis of the references. In any event, applicants argue: "Ahrens provides

for *in vitro* responses of progenitor cells to a group of osteoinductive compounds, which include *inter-alia* a BMP" (sentence bridging pages 9 and 10 of the response). This is a mischaracterization of the studies performed by Ahrens. It is true that Ahrens stimulates the cells expressing BMP-2 or BMP-4 with ascorbic acid and β-glycerophosphate (Ahrens page 872, column 1), but it is clear that osteogenic potential of the cells is due to the expressed BMP-2 or BMP-4, and that the two stimulatory factors are not sufficient to lead to osteogenesis. Control cells not expressing either BMP fail to show any sign of osteogenesis when treated with these two factors. Thus it is the indeed the presence of the BMP that leads to and permits osteogenic potential (see Figures 4 and 5). Having shown the osteogenic potential of these cells when transfected with BMP-2 or BMP-4, delivery of these cells using the methods of Bonadio would lead the skilled artisan to believe there would be a high likelihood of successful bone repair.

18. The response also asserts that: "Bonadio does not credibly provide foundation that BMP gene transfer provides more than paracrine effects for healing a bone infirmity"(response page 8, first paragraph). The Office Action of 6/15/04 successfully addresses these concerns on pages 6 and 7.

19. Applicants' arguments regarding the unexpected benefits of *ex vivo* therapy have been addresses above.

20. Applicants' arguments pertaining to claims 27 and 28, i.e. Wozney and Hattersley, respectively, essentially only argue that neither Wozney nor Hattersley correct the alleged deficiencies in combining Ahrens with Bonadio and Lee. In view of the above arguments, the arguments regarding Wozney and Hattersley are not persuasive.

21. Thus, considering all evidence presently of record, the only conclusion that seems possible is that the rejections under 35 U.S.C. 103 are proper and should be maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

JAMES KETTER
PRIMARY EXAMINER